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(71) *Sökande* / *Applicant (s)* — *AstraZeneca AB, Södertälje SE*

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Sonia André

Avgift
Fee

PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

New Process

The present invention relates to a new process for the preparation of combinations of drugs, in particular combinations of corticosteroids and inhaled β_2 agonists.

It is known that some pharmaceutical compounds suitable for administration via pressurised metered dose inhalers (pMDI's) have a tendency to adhere to the container surface and surfaces of the manufacturing vessel and filling equipment. This makes filling of the metered dose inhaler container and subsequent dosing from those containers, less uniform. The problem has traditionally been overcome by adding an overage to the formulation, i.e. adding more of one or more of the ingredients than is theoretically required. However the effect cannot always be consistent enough for the overage method to alleviate the problem and, in the case of expensive drug compound, can add to the cost of the final product.

In a first aspect the invention therefore provides a process for the preparation of a pharmaceutical formulation, which comprises addition of two or more components in a stepwise manner to minimise loss of one or more of the components through adhesion to equipment surfaces.

This invention particularly applies to formulations where the drug or drugs which have a tendency to adhere to the surfaces of the manufacturing equipment in which they are mixed and through which they are dispensed into the container.

Also this invention particularly applies to the manufacture of suspension formulations and most preferably to that of drug suspended in a hydrofluoroalkane propellant. Preferred propellants are HFA 134a and HFA 227 and mixtures thereof.

Preferably the drugs of the invention are budesonide and formoterol or a hydrate of a salt thereof, in particular formoterol fumarate dihydrate.

Preferably the budesonide is added prior to the addition of the formoterol fumarate dihydrate.

The process of addition significantly reduces the formoterol that is lost during manufacture such that the manufacturing overages are significantly reduced.

Suitably the molar ratio of the budesonide to the formoterol fumarate dihydrate is from 2500:1 to 1:12.

The molar ratio of the budesonide to the formoterol fumarate dihydrate is preferably from 555:1 to 1:2 and more preferably from 150:1 to 1:1. The molar ratio of the budesonide to the formoterol fumarate dihydrate is even more preferably from 133:1 to 6:1. The molar ratio of the budesonide to the formoterol fumarate dihydrate is most preferably 50:1 to 6:1).

In a further aspect the invention provides a pharmaceutical formulation prepared according to the above process and the use of such a formulation in therapy in particular the treatment and prophylaxis of respiratory disorders such as asthma and COPD.

The invention also provides a method of treating asthma or COPD which comprised administering to a patient in need of such treatment a formulation as defined and prepared above.

The formulations prepared according to the invention optionally comprise one or more pharmaceutically acceptable suspending agents, valve lubricants , flavourings, bulking agents , sweetners or cosolvents., . The formulations are preferably in the form of a micronised powder for inhalation suspended in a hydrofluoroalkane propellant, wherein the particles of the pharmaceutically active ingredients have a mass median diameter of less than 10 μm.

The invention is illustrated by the following examples

The examples shown below are of four batches produced at the commercial manufacturing site. The methodology of the production is known in the art (details later). However the principal could equally apply to equipment of smaller surface area.

The amount of the active ingredients in the resulting pMDI's was assayed and compared to theoretical.
The resulting API concentration was determined by Total Can Assay. The differences seen cannot be attributed to error in assay results due to analytical variation(RSD 0.9%)

The results for each batch show the overage of Formoterol added, the theoretical amount expected if no loss occurs, the resulting assay figure and the API added first.

Examples

Batch	% Overage	Order of Addition	Theoretical FFD % w/w	Actual FFD % w/w found on assay	% Difference between theoretical and actual
1	4.3	FFD 1st	0.0073	0.0068	6.8 %
2	4.3	FFD 1st	0.0073	0.0068	6.8 %
3	0	FFD 1st	0.0069	0.0066	4.3 %
4	3.4	BUD 1st	0.0071	0.0071	0 %

Conclusion

The addition of Budesonide prior to the addition of Formoterol reduces the amount of Formoterol that is lost during manufacture such that the manufacturing overages are significantly reduced.

The advantage over random addition is that this method makes the outcome of the final API concentration more consistent and reduces cost.

Claims

1. A process for the preparation of a pharmaceutical formulation, which comprises addition of two or more components in a stepwise manner to minimise loss of one or more of the components through adhesion to equipment surfaces.

2. A process according to claim 1 in which the formulation components are active drug substances.

3. A process according to claim 1 or 2 in which the components are budesonide and formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

4. A process according to claim 1 or 2 in which the components are budesonide and formoterol fumarate dihydrate.

5. A process according to claim 4 in which the budesonide is added prior to the formoterol fumarate dihydrate.

6. A process according to claim 4 or 5 in which the molar ratio of the first active ingredient to the second active ingredient of from 2500:1 to 1:12.

7. A pharmaceutical formulation prepared according to the process defined in any one of claims 1 to 6.

8. A formulation according to claim 7 which is in the form of a suspension.

9. A formulation according to claim 8 in which the drugs are suspended in one or more HFA propellants.

10. A formulatin according to claim 9 in which the HFA propellants are HFA 134a or HFA 227 or a mixture thereof.

11. Use of a formulation according to any one of claims 7 to 10 for the treatment or prophylaxis of asthma or COPD.

12. A method of treating asthma or COPD which comprised administering to a patient in need of such treatment a formulation according to any one of claims 7 to 10.

Abstract

The invention relates to a new process for preparing formulations of glucocorticosteroids and long-acting β2-agonists.